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Comparative Toxicity of PCBs and Related Compounds in Various Species of Animals

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There are several basic principles that apply to the clinicopathologic syndrome produced by polychlorinated biphenyls (PCBs). They are as follows: The degree of halogenation and position of the halogen atoms determine the potency of PCB, PBB, CDD, CDF and CN; in a given species of animals, the clinicopathologic syndrome induced by PCB is comparable to that induced by polybrominated biphenyls (PBB), chlorinated dibenzo-*p*-dioxins (CDD), chlorinated dibenzofurans (CDF), and chlorinated naphthalenes (CN) when an equitoxic dose is achieved; The clinicopathologic syndrome is different in each species of animals; Different species of animals vary in their susceptibility to intoxication; intoxication is more readily effected in young animals that in adults; at lethal doses the time between exposure and death is prolonged (>2 weeks).

Relative Potency of PCBs, CDDs, CDFs and CNs

It is sometimes difficult to establish which of the subject compounds is the most toxic because, with the exception of the laboratory environment, most "natural" exposures are to mixtures of several isomers. In addition, because of chemical processes used in the manufacture of these chemicals or of chemicals in which they are found as contaminants, more than one class of compound may be involved in a "natural exposure." For example, it has been shown that the PCBs involved in "Yusho Disease" were contaminated with CDFs (*1*) and PBBs were contaminated with brominated naphthalenes (*2*). Similarly, phenoxy herbicides have been contaminated with CDFs as well as CDDs.

To establish clearly the relative toxicity of each class of compound would require the study of the most toxic isomer of each class in the same animal species using the same experimental conditions. This has been done *in vivo* (*3,4*) and *in vitro* (*5,6*). The results of these investigations show a relative ranking of toxicity as follows: CDD (most toxic) > CDF >> PCB > CN. These authors have also demonstrated that a brominated isomer is somewhat more toxic than its chlorinated counterpart. To further add to the complexity of this subject it appears that the various isomers and/or classes may act in an additive or synergistic manner to each other (*7*).

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These findings suggest that it is inappropriate in most "natural exposures" to attempt to equate the toxic manifestations of the exposure to a single isomer or congener or chemical class unless it has been clearly shown that the exposure was restricted to that isomer or class of compound.

Species Sensitivity

There is a considerable difference in the sensitivity of various species of animals to these compounds. However, in most cases, if a given species is more sensitive than another to a given class of compound, i.e., PCB, this species of animal will also be more sensitive to the other classes, i.e., CDDs, CDFs, etc. It has also been observed that in most instances in regard to the dose of a given isomer or class of chemical, young animals are more sensitive than adults and females more sensitive than males.

While there are a limited number of studies where the protocols are comparable, the general impression is that chickens (and possibly other avian species) and guinea pigs are the most sensitive species of animals to intoxication with these classes of chemicals (Table 1). In contrast, hamsters and amphibians appear to be fairly resistant to the toxic effects, at least to TCDD.

Clinical Signs

The clinical signs of intoxication in animals from exposure to these classes of compounds can be divided into acute and chronic. At acutely lethal doses the main clinical sign in most species of animals is a progressive

Table 1. Lethal dose (LD_{50}) of 2,3,7,8-TCDD in various animal species.

Animal/strain	Sex	Route	Observation period	LD_{50}, μg/kg	Comments	Reference
Guinea pig, Hartley Strain	M	Gavage	8 weeks	0.6	Time to death 5–34 days	(*31*)
Rats/Sherman	M	Gavage	8 weeks	22	Time to death 9–27 days	(*31*)
Rats/Sherman	F	Gavage	8 weeks	45	Time to death 14–43 days	(*31*)
Monkey/rhesus	F	Gavage	10 weeks	<70	Time to death >35 days	(*3*)
Mice/C57B1	M	Gavage	60 days	114	Time to death 15–20 days	(*32*)
	M	Gavage	30 days	284	Time to death 22–25 days	(*3*)
Rabbits/NZ	M	Gavage	8 weeks	115	Time to death 6–39 days	(*31*)
Hamster	M	Gavage	55 days	5051	Time to death 26–43 days	(*33*)

loss of body weight followed by weakness, debilitation, and finally death. This is accompained by decreased food and water intake which accounts for some (*8*) but not all of the weight loss (*3*). These may be the only signs observed in rats, mice, guinea pigs, rabbits, mink, and poultry after oral administration. However, skin lesions have been reported in hairless mice (*9*), and acnelike lesions have been described in the ears of rabbits after local application (*10*). At times, poultry may show a terminal increase in body weight due to accumulation of body fluids (subcutaneous edema, ascites, hydrothorax and hydropericardium) (*11*). It is noteworthy that the time to death in most species is from several days to weeks even at super lethal exposures (*12*).

It is difficult to describe acute signs of toxicity in non-human primates because they do not die "acutely." The time to death is from one to three months even at doses several times the LD_{50}. In addition to body weight loss, the clinical syndrome in monkeys (*13*) and cattle (*14*) is characterized by skin and eyelid lesions and abnormal finger or toe nails or hooves. The lesions in monkeys are follicular dermatitis (acne) of the face, neck, and forearms, enlarged tortuous Meibomian glands in the eyelid and overgrowth and loss of nails of the hands and feet. Alopecia may be present, particularly in the areas of the body showing dermatitis. The skin of cattle is thickened and dry, particularly over the neck, shoulders and back. The hooves of intoxicated animals may be overgrown with associated lameness.

Signs of poor fertility and fetal wastage are hallmarks of the disease syndrome in chronic sublethal exposures. These may be the main clinical features in "natural" exposures, particularly in monkeys (*15*), mink (*16*) and cattle (*17*). The reproductive problems appear to be primarily attributable to the female in these species. This may be related to the fact that in these species of animals, females are more sensitive than males to intoxication of these classes of chemicals. Also, young animals are more sensitive than adults (*12*).

Organ Weights

In those studies where organ weights have been measured, there are two organs that show a weight effect in most species of animals (*12*). The thymus shows a dramatic decrease in weight (actual and relative to body weight), often only 25% of normal. In contrast, the liver is usually increased in weight. A decrease in the weight of the gonads has been reported but this may be a reflection of debilitation rather than a direct effect. A similar explanation may appropriate for the mild increase in the weight of the adrenal gland since it has been observed at only doses approaching the LD_{50}.

Hematology

Hematological changes appear to be directly related to lesions in the bone marrow (atrophy), which occur in all species of animals studied at high (lethal) exposure levels. In acute studies (<30 days), thrombocytopenia (*18*) and lymphopenia have been reported in several species of laboratory animals. Increased erythrocyte counts have been reported in acute studies but this may be related to terminal dehydration which is a consistant finding in lethally exposed animals.

In chronic studies, the most consistent hematologic finding is a mild to moderate degree of anemia (*12,19*). The white blood cell picture is more complex after long term exposure. Some studies show decreases in specific types of leukocytes while other studies show a leukocytosis. The most plausible explanation for this disparity of results is the presence of secondary infections. The confounding issue of secondary disease has most clearly been documented in environmental (outside the laboratory) exposures, such as the PBB incident in Michigan (*17*) and in various PCB/CDF exposures in primate facilities (*15*).

Clinical Chemistry

The study of blood serum changes is one of the more complex features of intoxication from these compounds. The reason for this is that the changes in the serum components reflect lesions in all parts of the body. Since the spectrum of anatomic pathology varies between species, it is not surprising that serum chemistry findings also vary since they reflect those lesions. As an example, increases in serum glutamic-oxaloacetic (GOT) and glutamic-pyruvate (GPT) transaminases and lactic dehydrogenase (LDH) were reported in TCDD exposed rats (*18*) but not in guinea pigs equally intoxicated (*3*). This is readily explained by the fact that rats show a

Table 2. Summary of lesions in various species of animals.

Species	Lesion severity[a]					
	Thymus	Liver	Gall bladder	Stomach	Urinary tract	Skin
Guinea pig	+ 3	±	—	—	+ 3	—
Mouse	+ 3	+ 2	—	—	—	+ 2[b]
Rat	+ 3	+ 2	NA	+ 1	—	—
Hamster	+ 3	+ 1	+ 2	—	+ 2	+ 1
Chicken	+ 3	+ 3	—	+ 1	—	—
Rabbit	+ 3	+ 3	—	—	—	+ 3[c]
Monkey	+ 3	+ 1	+ 3	+ 3	+ 2	+ 3
Cattle	+ 2	+ 1	+ 2	—	+ 2	+ 1

[a]Severity: ± = minimal; + 1 = mild; + 2 = moderate; + 3 = marked; NA = not applicable.
[b]Present in some strains but not others.
[c]Present in ear after local application.

significant amount of liver pathology while it is minimal in guinea pigs.

Changes in serum lipid have received considerable attention in studies of these compounds. Rats exposed to TCDD exhibit hyperlipidemia because of increases in cholesterol and high density lipoproteins (HDL). No change was observed in low-density lipoproteins (LDL) or triglycerides (*20*). In contrast, similarly intoxicated guinea pigs show an increase in triglycerides and LDL as well as other lipids.

Decreases in total serum protein, due primarily to a reduction in the albumin fraction have been reported in severely intoxicated guinea pigs and mice (*3*). Changes have also been reported in specific globulin fractions. It is interesting that mice exposed to a low level of TCDD had increased serum globulins, but decreased levels at a higher dose (*21*). These abnormalities have been related to lesions of the liver and immune system. Functional abnormalities of the immune system have also been described but are reported in a separate paper in these proceedings.

Anatomic Pathology

The macroscopic and microscopic changes induced by these classes of chemicals have been reviewed previously (*12*). There are two general concepts regarding the lesions produced by these chemicals: (1) the pathologic syndrome is essentially the same within a given animal species for all of these compounds once a toxic is achieved; (2) the pathologic syndrome varies in different species of animals (Table 2).

The organ which is consistently affected in all species is the thymus (*12*). Additionally, it usually shows changes at doses lower than those required to cause lesions in other organs. The primary lesion is a loss of cortical lymphocytes. In animals lethally exposed to these compounds only a remnant of the cortex may be present. This is often accompanied by necrotic debris in the medulla. At less toxic doses the thymus may look normal histopathologically while being one half normal size. This is why organ weights are a necessity in evaluating the toxicopathology of these chemicals.

The liver varies in its response to these classes of chemicals. In all avian species studied (*22*) and in rabbits (*10*), severe necrosis and hemorrhage are the hallmarks of lethal intoxication. In fact, death in these species has been ascribed to severe liver pathology. Prominent but lesser degrees of pathology are observed in rats and mice while the liver is only minimally damaged (anatomically) in guinea pigs, cattle, and monkeys (*12*). Intrahepatic bile duct hyperplasia has been described in rodents and monkeys but is a more prominent feature in chronically exposed animals.

Marked epithelial hyerplasia of the extrahepatic bile duct and gall bladder have been described in monkeys (*13*) and cattle (*23*). The height and number of epithelial cells is increased but more striking is the papillary appearance of the mucosa. It is so prominent that macroscopically the bile duct may be two to three times its normal diameter. Epithelial erosions, ulcers and inflammation are often part of the lesion.

Hyperplasia of the epithelium lining the urinary tract has been described in guinea pigs, cattle and monkeys (*12*). The lesion extends from the renal pelvis to the urinary bladder stopping at the level of the urethra. The histologic appearance of the epithelium appears normal in all respects except that the number of cell layers is increased. The parenchyma of the kidney does not show lesions, although an increased severity of chronic progressive nephropathy (a common disease related to aging) has been described in rats exposed chronically to PCBs (*24*) and PBBs (*25*).

The stomach of monkeys exposed to these classes of chemicals exhibits a lesion which may be pathognomonic and has been referred to as "simian gastropathy" (*26*). In acute lethal exposures, the chief (acid-producing) cells are replaced by hyperplastic mucous producing cells. In more chronic exposures, the hyperplasitc change becomes more pronounced and at times appears to invade subjacent tissues. Whether this represents true invasion is questionable, since it is usually admixed with ulcerative processes and inflammatory changes. The lesion may be so prominent that macroscopically it often appears as a fungoidlike mass suggesting neoplasia. However, the lesion has never been shown to metastasize and will regress if exposure to those chemicals with a relatively short biological half-life ceases (*27*). It should be emphasized that some of these compounds (and congeners thereof) have an extremely long biological half-life and even though "external" exposure is stopped the host is still effectively being exposed via the compound stored in its body. A similar but much less severe lesion has been described in rats exposed to PBBs (*25*). The large intestine also shows hyperplastic changes in monkeys chronically exposed to these chemicals (*28*).

The skin and associated structures of monkeys, rabbits (ears), and certain strains of mice show characteristics lesions when the animals are exposed to these classes of chemicals. In monkeys the lesion is characterized microscopically by mild epithelial hyperkeratosis

and severe atrophy of sebaceous glands and hyperkeratosis of their ducts (*13*). The ducts become occluded with keratinaceous debris and grossly the lesion mimics an acnelike lesion. This lesion is commonly observed on the face, particularly on or near the nose but may be found on other areas of the body. A similar lesion is observed in the Meibomian glands of the eyelid and ceruminous glands of the external suditory canal. These modified sebaceous glands are severely affected and may be the most sensitive clinical indicators of intoxication. Alopecia and dry scaly skin are also features of exposure in monkeys.

While most strains of mice do not show skin lesions, certain "hairless" (actually not hairless since remnants of follicles are present) strains show a similar skin lesion to that in monkeys (*29*). Again, the lesion appears to be related to atrophic and hyperkeratotic changes in the sebaceous glands and their ducts. The inner surface of a rabbits ear also shows acnelike lesions if these compounds are applied directly to the surface. In fact, this lesion provides a fairly rapid (7–14 days) bioassay for the detection of these classes of chemicals (*30*). Cattle also show a characteristic skin disease when exposed to these compounds. Historically, one of the earliest environment intoxications of these classes of chemicals involved dairy cattle which showed severe hyperkeratosis, particularly on the face, neck and over the shoulders. The disease was caused by exposure to CNs in axle grease which the cattle ingested (*14*).

Accumulation of fluid in the subcutis, abdominal cavity, thorax and pericardial sac is a characteristic feature of intoxication in avian species. The original recognition of a possible dioxin problem in animals was a disasterous episode in chickens which was referred to as chick edema disease (*11*). It resulted in the death and destruction of hundreds of thousands of chickens and eggs.

Other lesions have been ascribed to intoxication with these classes of chemicals (*120*. These include hemorrhage of the adrenal, atrophy of the zona glomerulosa of the adrenal cortex, germ cell atrophy of the testicle and ovary and amyloidosis. Whether these are primary effects or merely a reflection of severe cachexia in severely intoxicated animals or exacerbation of aging lesions is debatable. These lesions are observed primarily in animals which die or which are killed in a moribund condition. In addition, similar lesions are found in animals extremely sick from other causes or in aged animals.

The carcinogenic potential of these chemicals is described in other portions of these proceedings.

Discussion

The clinicopathologic syndrome associated with exposure to these classes of chemicals is fairly characteristic for each species of animals. Unfortunately, in a diagnostic situation it is impossible to differentiate between PCBs, CDDs, CDFs, PBBs or CNs. Diagnosis is also confounded in many instances by the presence of secondary infectious disease(s). Chemical analysis of tissue samples is required for a definitive etiological diagnosis. Even then, it is usually impossible to ascribe the severity of intoxication to a given level of the chemical in various tissues. In most cases, the presence of the chemical in tissues means only that the animal was exposed. The presence of the characteristic clinicopathologic syndrome is required for a presumptive diagnosis of intoxication. For this reason, a careful post mortum examination is required with collection of an appropriate set of tissues.

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